REMARKS

Claims 1 to 40 and 42 to 53 appear in this application for the Examiner's review and consideration. Claims 1 to 32, 39, 40, and 46 to 53 have been withdrawn from consideration, as being drawn to non-elected subject matter. Claims 33-38 and 42-45 are currently rejected. Claims 44 and 45 have been amended and new claims 54 and 55 have been added. Support for the amendments and new claims can be found in the specification on page 7, first paragraph. Further, submitted herewith is a declaration by Claude Singer regarding comparative results obtained with respect to the Kato et al reference (U.S. 6,002,011).

1. Claims 33-38 and 42-45 are rejected under 35 U.S.C. 102(a), (b) and/or (e) as being anticipated.

The Examiner has rejected claims 33-38 and 42-45 as being anticipated by Vercer et al., Kotar et al., Choi et al., Nohara et al., Kato et al., and Avrutov et al. I, and II. According to the Examiner the cited references specifically disclose the claimed compound and compositions. Further, in response to Applicants' arguments, the Examiner asserts that Applicants have failed to show any unobvious propeties vis-à-vis the prior art compounds cited in the references of record. According to the Examiner, Applicants admit that their compounds are not pure compounds and no objective evidence has been presented establishing any unobvious properties for the claimed impure compounds vis-à-vis the impure prior art compounds. Thus, the Examiner asserts allegations by Applicants do not take place of objective evidence showing that the alleged "stable" compound is any different from the prior art.

In response, Applicants submit that, as recited in claims 33 to 38, the presently claimed invention is directed to a **chemically stable** lansoprazole, prepared by the process of the invention. As recited in claims 42 and 43, the presently claimed invention is directed to a **chemically stable** lansoprazole, comprising less than about 0.1% (wt/wt) sulfone derivative and less than about 0.1% (wt/wt) sulfide derivative, upon exposure to a relative humidity of 75% at 40°C for a period of at least about three months and for a period of at least about six months, respectively. As recited in claims 44 and 45, the presently claimed invention is directed to a **chemically stable** lansoprazole that does not change color upon exposure to a relative humidity of 75% at 40°C for a period of at least about three months.

In contrast to the Examiner's assertions, as demonstrated by objective evidence in Examples 2 and 3 of the present specification and the attached declaration by Claude Singer,

the presently claimed stable lansoprazole is substantially more chemically stable than prior art lansoprazole. As previously submitted, in example 2 of the specification it is shown that after one month at a temperature of 40°C and a relative humidity of 75 percent, none of the sulfone compound can be detected in the claimed chemically stable lansoprazole, which remains white. In contrast, after one month under the same conditions, the non-stabilized, lansoprazole contains 0.03 percent of the sulfone compound, and has changed color. Similarly, in example 3 of the specification it is shown that after three months at 40°C and a relative humidity of 75 percent, the chemically stable lansoprazole composition of the invention contains only 0.03 percent of the sulfone compound, and remains white. In contrast, under the same conditions, the non-stabilized lansoprazole contains 0.06 percent of the sulfone compound, and has changed color. Moreover, Applicants submit that, as observed by Singer, the results in the Singer declaration, submitted herewith, show that after three months at a temperature of 40°C and a relative humidity of 75 percent, lansoprazole prepared both according to example 1 and comparative example 1 in the Kato et al reference, contain 0.14% (w/w) or 0.17% (w/w) of the sulfone impurity and 0.14% (w/w) or 0.34% (w/w) of the sulfide impurity and show a brownish discoloration and therefore lack the stability of lansoprazole as in the claimed invention.

Although the cited prior art references may disclose lansoprazole and polymorphs of lansoprazole, the references disclose non-stable, prior art lansoprazole, not the presently claimed chemically stable lansoprazole composition.

As previously submitted, in contrast to the presently claimed invention, Vrečer, Kotar, Choi, Nohara, and Avrutov I and II disclose non-stable prior art lansoprazole for the reasons on record. In addition, the process of preparing lansoprazole in Kato (the '011 patent) represents a process which may be considered the closest prior art to the process required to stabilize lansoprazole as in the current invention, but which does not provide the claimed stable lansoprazole as shown in the Singer declaration submitted herewith.

Kato does not disclose a lansoprazole composition, having long term **chemical stability**, i.e., for over three to six months, as does the presently claimed chemically stable lansoprazole composition, which is stabilized by isolating and/or drying the lansoprazole composition in the presence of a relatively large amount of a weak base, such as ammonia. The process in Kato only uses a small amount of ammonia as previously submitted. Moreover, as observed by Singer the results in the Singer declaration show that lansoprazole prepared according to Kato is not stable upon longterm storage. In the Singer declaration

data are presented wherein lansoprazole prepared according to Example 1 and Comparative Example 1 are stored for three months at 40°C and 75% relative humidity. Upon storage the lansoprazole prepared according to Kato shows an increase in the impurities particularly in the sulfide impurity and also shows discoloration from an initially white material to a brownish material. As discussed above in the claimed stable lansoprazole such increase in impurities is not observed nor is a discoloration observed. For these reasons, Applicants submit that the lansoprazole prepared by the processes disclosed by Kato is chemically unstable during storage. Therefore, Kato does not disclose the presently claimed chemically stable lansoprazole composition, and, thus, Kato does not anticipate the present claims.

Therefore, as none of Vrečer, Kotar, Choi, Nohara, Singer, Kato, and Avrutov disclose the presently claimed invention of **chemically stable** lansoprazole, the present claims are not anticipated by those references. Accordingly, it is respectfully requested that the Examiner withdraw the rejection of claims 33 to 38 and 41 to 45 under 35 U.S.C. §102(a), (b), and/or (e).

2. Claims 33-38 and 42-45 were rejected under 35 U.S.C. 103(a) as being obvious.

The Examiner has rejected claims 33-38 and 42-45 as being obvious over the combined teachings of Vercer et al., Kotar et al., Choi et al., Nohara et al., Kato et al., and Avrutov et al. I, and II in view of Hableblian et al., Chemical & Engineering News, US Pharmacopeia, Muzaffar et al, Jain et al, Taday et al, Concise Encyclopedia Chemistry and Brittain et al. (Polymorphism in Pharmaceutical Solids, pages 1-2, 185). Again, according to the Examiner the cited primary references teach the stable crystal forms of the instant known compound and as well as the pharmaceutical compositions. In addition, the Examiner asserts that the remaining references teach that compounds exist in different crystalline forms and that at any particular temperature and pressure only one crystalline form is thermodynamically stable. The Examiner alleges that hence the claimed crystalline form as well as its relative selectivity of properties vis-à-vis the known compound are suggested by the references. According to the Examiner it is obvious in view of the references that the compound would exist in **different stable crystalline forms** and no unexpected or unobvious properties are noted. In addition, in response to Applicants arguments, the Examiner asserts that no objective evidence is provided establishing that the claimed stable compound is any more stable than the prior art compounds cited in the references of record.

In response, Applicants submit that the claimed invention is directed to a **chemically stable** lansoprazole whether crystalline or not. The method of preparing the chemically stable lansoprazole, presently claimed contains a crystallization step. However, the claimed invention is not a particular, **thermodynamically stable**, crystalline form of lansoprazole but a **chemically stable** lansoprazole. Lansoprazole is chemically instable because of its inclusion of solvent (such as water) when crystallized. The chemically instability of solvated lansoprazole is attributed to proton attack of lansoprazole at the sulfur atom resulting in the appearance of its derivatives, the sulfide derivative 2-[[3-methyl-4-(2,2,2-trifluorethoxy)-2-pyridinil]thio]-1H benzimidazole and the sulfone derivative 2-[[3-methyl-4-(2,2,2-trifluorethoxy)-2-pyridinil]sulfonyl]-1H benzimidazole, which are considered impurities and chemically distinct from 2-[[[3-methyl-4-(2,2,2-trifluoro-ethoxy)-2-pyridinyl]methyl] sulfinyl]-*1H*-benzimidazole. The presently claimed invention is directed to lansoprazole which is stable, i.e. is less prone to chemically instability, and the specification specifically discloses the claimed compound and compositions. Moreover, in examples 1 and 2 of the current specification Applicants provide objective evidence of the unexpected stability of the claimed lansoprazole over unstable prior art lansoprazole, prepared by a different process. In addition, the Singer declaration, submitted herewith, further provides evidence that the lansoprazole obtained according to the process in the Kato reference fails to show the same stability.

None of the cited references disclose or suggest the chemically stable lansoprazole composition of the presently claimed invention. As previously discussed, Vrečer, Kotar, Nohara, Kato, and Avrutov disclose either the relative physical stability of polymorphic forms or purified forms of lansoprazole, but do not teach or suggest a chemically stable lansoprazole composition, as presently claimed.

Further, Kato discloses a substantially solvent-free lansoprazole that is free of decomposition in the course of vacuum drying. Kato does not disclose or suggest a lansoprazole, having chemical stability over three to six months, as does the presently claimed chemically stable lansoprazole composition. In fact, as observed by Singer, the results described in the Singer declaration show that in the lansoprazole of Kato (prepared according to the processes in example 1 and comparative example 1), stored for three months at 40°C at 75% relative humidity, increased amount of the impurities can be detected. In particular, an increased amount of the sulfide impurity can be detected. The Singer declaration also shows that the lansoprazole of Kato shows discoloration, another sign of

decomposition and instability, upon storage for three months at 40°C at 75% relative humidity. The stored lansoprazole obtained according to Kato showed brownish discoloration upon storage. Therefore, Kato does not teach or suggest the presently claimed **chemically stable** lansoprazole composition.

As stated in the Office Action, Hableblian, Muzaffar, Jain, and Taday each teach that some crystalline compounds can exist in different crystalline forms. The Office Action also states, at page 4, that C & E News, Muzaffar, U.S. Pharmacopia, and Concise Encyclopedia of Chemistry all teach that, at any particular temperature and pressure, only one crystalline form is thermodynamically stable.

However, as discussed above, the presently claimed invention is directed to a **chemically stable** lansoprazole composition, **not a thermodynamically stable** polymorphic form. None of the cited references whether taken alone or in combination, disclose or suggest the presently claimed chemically stable lansoprazole composition. Instead, the cited prior art references discloses only non-stable, prior art lansoprazole or thermodynamically stable polymorphs thereof. Applicants submit that thermodynamic stability of polymorphs of an active pharmaceutical ingredient (here lansoprazole) is very different and not necessarily related to chemically stability of such compound.

Therefore, as the cited references, whether taken alone or in combination do not disclose or suggest the presently claimed invention, the claims are not obvious over these references. Accordingly, it is respectfully requested that the Examiner withdraw the rejection of claims 33 to 38 and 41 to 45 under 35 U.S.C. §103(a).

3. Claims 36-38 were rejected under 35 U.S.C. 112, first paragraph.

Claims 36 to 38 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement, for the reasons set forth on pages 5 to 7 of the Office Action.

In particular, the rejection is based on the possibility of a change in polymorphic state of a crystalline form of a compound during storage or tablet preparation. The Examiner asserts that there is a lack of description as to whether the compositions are able to maintain the compound in the stable form claimed. According to the Examiner, processing a compound into a pharmaceutical composition could create a different form than the crystalline form being claimed. According to the Examiner the specification fails to describe the pharmaceutical compositions claimed in terms of their X-ray diffraction pattern or

infrared spectrum data. Further, the Examiner asserts that Applicants have failed to provide any objective evidence that the instant stable form is indeed maintained in the compositions. According to the Examiner the claimed compounds behave similarly to polymorphs and that the prior art of record clearly show that processes for preparing pharmaceuticals causes changes. For these reasons the Examiner asserts that the specification lacks direction or guidance for placing all of the alleged products in the possession of the public without inviting more than routine experimentation. Further, the Office Action, at page 7, states

> The specification fails to disclose the X-ray diffraction pattern and infrared spectra of the asserted stable compound or compositions containing the stable form. Polymorphs often change into other forms during drug manufacture into a pharmaceutical composition. Based on the unpredictability in the art, the applicant is not entitled to the X-ray diffraction patterns claimed for the compounds and pharmaceutical compositions.

Further, according to the Examiner, "in absence of any description or factual evidence, how a crystalline form can be maintained in a composition to minimize transformation, no assumption can be made that the alleged stable form will be maintained upon compression, tableting, etc ....

In response, Applicants respectfully submit the Examiner's rejection is unclear considering that according to the Examiner the claims fail to comply with the written description requirement while at the same time discussing the *Wands* factors relating to enablement. Further, the Examiner asserts that the specification lacks direction or guidance for placing all of the alleged products in the possession of the public, whereas for the claims to comply with the written description requirement, the claimed subject matter needs to be described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants, submit that the presently claimed invention is directed to **chemically stable** lansoprazole as is clearly described in the specification including examples providing evidence of the stability of the claimed stable lansoprazole. Processing of a chemically stable active ingredient into a pharmaceutical composition would not change the chemical stability of the active pharmaceutical ingredient in a manner as suggested by the Examiner with respect to polymorphic forms. At pages 1 to 3, the present specification discusses the instability of prior art lansoprazole. As will be understood by one of ordinary skill in the art, the instability of lansoprazole discussed in the specification is not a polymorphic instability. Instead, the instability discussed in the specification is a chemical instability, the conversion

of the lansoprazole compound to other chemical compounds such as its sulfide or sulfone derivative. When prior art lansoprazole is stored or exposed to heat and humidity, a chemical change occurs, producing impurities in the form of different chemical compounds, not different polymorphic forms. At page 3, lines 1 to 11, the present specification states that during storage, prior art lansoprazole degrades, such that the concentration of lansoprazole decreases, resulting in discoloration. Degradation of a compound results from a chemical change, not a change in polymorphic form, as alleged in the Office Action. One of skill in the art, reading the specification, would clearly understand that the claimed invention is to a chemically stable lansoprazole in a pharmaceutical composition as it is supported by the specification, reasonably conveying to one skilled in the relevant art that the Applicants had possession of the claimed invention at the time the application was filed. Therefore, Applicants submit that claims 36-38 comply with the written description requirement.

Further, even if the rejection is an enablement rejection, as Applicants previously submitted XRD and IR spectra are not provided, and there is no teaching in the specification on how to maintain a particular polymorphic form because a new polymorphic crystalline form of lansoprazole is not disclosed or claimed in the present application. The presently claimed invention is directed to a **chemically stable** lansoprazole. That is, the presently claimed invention is a lansoprazole, produced in a known process, that is then stabilized according to the method of the invention, providing the chemically stable lansoprazole of the invention. As the present claims are not directed to a new polymorphic crystalline form, no XRD or IR spectral data are required. No disclosure of how to prevent the lansoprazole of the invention from converting to a different polymorphic form is provided, because the invention is **not** directed to a **polymorphic form**, or its thermodynamic stability.

Moreover, the present specification clearly teaches one of ordinary skill in the art how to make and use the invention. In the first paragraph of each of pages 2 and 7, the specification discloses the impurities that are formed in lansoprazole during synthesis and storage. The impurities are further disclosed in Tables 1 and 2 on pages 13 and 14, respectively. Processes for preparing the presently claimed chemically stable lansoprazole are set forth in both the Summary and Detailed Description sections of the specification, and are particularly exemplified in Examples 2 and 3 on pages 12 to 14 of the specification. The superior chemical stability of the presently claimed chemically stable lansoprazole, compared to the prior art lansoprazole, is set forth in the aforementioned Tables 1 and 2.

Clearly, one of ordinary skill in the art would understand how to make and use the presently claimed invention from the present specification.

With respect to an alleged lack of description as to whether the pharmaceutical carriers are able to maintain the compound in the stable form claimed, one of ordinary skill in the art, in light of the specification, would understand how to make and use the presently claimed pharmaceutical compositions. Pharmaceutical carriers, diluents, disintegrates, binders, giants, dyes, colorants, lubricants, excipients, and the like, useful in the invention, are set forth on pages 9 to 12. As discussed above, processing of a chemically stable active ingredient into a pharmaceutical composition would not change the **chemical stability** of the active pharmaceutical ingredient in a manner as suggested by the Examiner with respect to **polymorphic forms**.

Therefore, as the presently claimed invention is not directed to stable polymorphs, but, instead, is directed to a chemically stable lansoprazole, the present specification clearly teaches one of ordinary skill in the art how to make and use the claimed invention and reasonably conveys that applicants had possession thereof when the application was filed. Thus, the claims meet the requirements of 35 U.S.C. §112, first paragraph. Accordingly, it is respectfully requested that the Examiner withdraw the rejection of claims 36 to 38 under 35 U.S.C. § 112, first paragraph.

4. Claims 33-38 and 42-45 were rejected under 35 U.S.C. 112, second paragraph for being indefinite.

Claims 33 to 38 and 42 to 45 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for the reasons set forth on pages 10-12 of the Office Action.

According to the Examiner, claims 33-35 are improper product-by-process claims, as such claims are improper in the same application where it has been demonstrated that the compound in question may be described by means of a chemical structure.

In response Applicants submit that claims 33-35 are directed to a stable lansoprazole. Lansoprazole, is an active pharmaceutical ingredient which may include some amount of other chemical compounds, other than the pure chemical compound lansoprazole, such as the previously described impurities. Although the chemical compound 2-[[[3-methyl-4-(2,2,2-trifluorethoxy)-2-pyridinyl]methyl]sulfinyl]-1H benzimidazole (lansoprazole) can be described by its chemical structure the presently claimed stable lansoprazole, which comprises the chemical compound lansoprazole and small amounts of impurities, may not be

readily described by the chemical structure of the compound as it is required by the Examiner. Further, the level of impurities and the chemical stability of the claimed lansoprazole is a result of the process preparing the claimed product.

Moreover, Applicants submit that "[an] applicant may present claims of varying scope even if it is necessary to describe the claimed product in product-by-process terms. *Ex parte Pantzer*, 176 USPQ 141 (Bd. App. 1972)", see MPEP 2173.05(p)(I). The Examiner's reliance on *In re Hughes*, is misplaced here considering that, as in *Hughes*, the claimed subject matter may be of different scope from lansprazole reciting specific amounts of the impurties. The court in *Hughes* stated that "even if is shown that product can be broadly defined solely in terms of structure and characteristics ...., that where his product is incapable of description by product claims which are of different scope, applicant is entitled to product-by-process claims..." See, *In re Hughes*, 182 USPQ 106, 108 (CCPA 1974). For these reasons, Applicants submit that product-by-process claims 33-35 are proper.

With regard to the recitation of "containing" in claims 42 and 43, the Examiner asserts that such open-ended term allows for the inclusion of other parameters not contemplated by Applicants. In response, as Applicants previously submitted, one of ordinary skill in the art would understand that any given sample of the active pharmaceutical ingredient lansoprazole contains lansoprazole and some amount of impurities. Even with the presently claimed chemically stable lansoprazole, it is practically impossible to remove all impurities, although the amount of any impurities in the presently claimed chemically stable lansoprazole increases significantly more slowly during storage than does the amount in prior art lansoprazole. Thus, one of ordinary skill in the art would understand that the "stable lansoprazole" of the present invention is actually a lansoprazole composition that may contain various impurities, including the sulfone and sulfide derivatives recited in claims 42 and 43. Accordingly, contrary to Examiner's assertions Applicants did contemplate the inclusion of other parameters not recited in the claims and the Examiner has no contrary evidence either in the currently pending application nor in the general knowledge regarding active pharmaceutical ingredients. Thus, the present claims may be open ended, and meet the requirements of 35 U.S.C. § 112.

With regard to the recitation of the term "lansoprazole" in claims 33-38 and 42-45, the Examiner asserts that where the generic name lansoprazole is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with 35 U.S.C. § 112, second paragraph. The Examiner cites *Ex Parte Simpson*, 218 USPQ

1020 (Bd. App. 1982). According to the Examiner the claim scope is uncertain since the generic name cannot be used to properly identify any particular material or product. The Examiner asserts that a generic name is used to identify a source of goods, and not the goods themselves. The Examiner further asserts that contra to Applicants' arguments the name lansoprazole does not describe the chemical structure of the compound.

In response, Applicants submit that the term "lansoprazole" is not a trade name but a generic name for the chemical entity, which as discussed above in addition to 2-[[[3-methyl-4-(2,2,2-trifluoro-ethoxy)-2-pyridinyl]methyl] sulfinyl]-*1H*-benzimidazole comprises chemical impurities. Lansoprazole is an active pharmaceutical ingredient marketed under the trade name PREVACID in the United States. Applicants submit that the term lansoprazole identifies an active pharmaceutical ingredient comprising 2-[[[3-methyl-4-(2,2,2-trifluoro-ethoxy)-2-pyridinyl]methyl] sulfinyl]-*1H*-benzimidazole and chemical impurities, regardless of its source, as clearly understood by the skilled artisan. Therefore, the term lansoprazole in the claims clearly identifies and describes the claimed subject matter in claims 33-38 and 42-45.

With respect to the alleged lack of antecedent basis for the recited limitations in claim 45, the Examiner asserts that there is no basis for the term "six months" in claim 45. In response, Applicants submit that claim 44 from which claim 45 depends recites "for at least about three months," which includes the limitation of "at least about six months." Considering that a time period of six months or more is clearly included in a period of at least 3 months, the above identified recitation in claim 44 provides the necessary antecedent basis for the term "at least about six months" in claim 45.

Therefore, the claims particularly point out and distinctly claim the subject matter Applicants regard as the invention. Accordingly, it is respectfully requested that the Examiner withdraw the rejection of claims 33 to 38 and 42 to 45 under 35 U.S.C. §112, second paragraph.

5. Claims 33-38 and 42-45 were provisionally rejected under the judicially created doctrine of obviousness type double patenting.

Claims 33-38, and 42-45 are provisionally rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 1-7 and 29-38 of copending U.S. Application Ser No. 10/717,325 in view of Haleblian et al., Chemical &

Engineering News, US Pharmacopeia, Muzaffar et al, Jain et al, Taday et al, Concise Encyclopedia Chemistry and Brittain et al. (Polymorphism in Pharmaceutical Solids, pages 1-2, 185). According to the Examiner the stable compound and compositions are disclosed in this copending application. In response, Applicants wish to defer filing a terminal disclaimer until the currently pending claims are deemed allowable, at which time, Applicants intend to file a terminal disclaimer.

Applicants thus submit that the entire application is now in condition for allowance, an early notice of which would be appreciated. Should the Examiner not agree with Applicants' position, a personal or telephonic interview is respectfully requested to discuss any remaining issues prior to the issuance of a further Office Action, and to expedite the allowance of the application.

A separate Petition for Extension of Time is submitted herewith. Should any additional fees be due, however, please charge such fees to Deposit Account No. **11-0600**.

Respectfully submitted,

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